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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/321,247	05/27/1999	SI-YI CHEN	0443-2U2	6190

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EXAMINER
LOEB, BRONWEN

ART UNIT	PAPER NUMBER
1636	14

DATE MAILED: 04/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/321,247	CHEN ET AL.	
	Examiner	Art Unit	
	Bronwen M. Loeb	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24,29 and 33-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24, 29 and 33-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 May 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This action is in response to the amendment filed 31 January 2002 in which claims 8-17, 23, 24, 33, 35, 38 and 39 were amended and claims 25-28 and 30-32 were cancelled. It is noted that in Applicant's amendment on p. 5, it is stated that claims 1-16 were amended however no amendments to claims 1-7 were found in the amendment.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-24, 29 and 33-39 are pending.

Response to Amendment

1. The provisional rejection of claims 25-28 and 30-32 under 35 U.S.C. §101 as claiming the same invention as that of claims 43, 47-50 and 52-54 of copending Application No. 09/332,275 has been withdrawn in view of Applicant's amendment.

The rejection of claims 8-16, 19 and 23-39 under 35 U.S.C. §112, second paragraph, as being indefinite has been withdrawn in view of Applicant's amendment.

The rejection of claims 17, 23, 24 and 32 under 35 U.S.C. §102(e) as being anticipated by Leavitt et al (USP 5,939,538) has been withdrawn in view of Applicant's amendment.

2. Claims 1, 2, 5-16, 18-22, 29, 33-35 and 38 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3, 6, 8-16, 18-20, 23, 26, 28-36, 38-42, 44-46 and 51 of copending Application No. 09/332,275 for the reasons of record and as further discussed below.

Claims 1-24, 29 and 33-39 stand rejected under 35 U.S.C. §112, first paragraph, lack of enablement for the reasons of record and as further discussed below.

3. New grounds of rejection are presented below.

Response to Arguments

4. With regard to the provisional rejection of claims 1, 2, 5-16, 18-22, 29, 33-35 and 38 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3, 6, 8-16, 18-20, 23, 26, 28-36, 38-42, 44-46 and 51 of copending Application No. 09/332,275, Applicant's arguments have been fully considered but are deemed not persuasive.

Applicant states that they agree to file a Terminal Disclaimer upon notice that the claims in the instant application and co-pending application 09/332,275 are allowable. In view of this, the rejection is maintained.

5. With regard to the rejection of claims 1-24, 29 and 33-39 under 35 U.S.C. §112, first paragraph, lack of enablement, Applicant's arguments have been fully considered but are deemed not persuasive.

On pages 7-18, Applicant argues the following points: there is no requirement for a working example; experimentation is allowed as long as it is not undue; there is no prohibition against broad claims; the specification is enabling because it provides extensive reduction to practice and extensive disclosure of techniques and assays and it is routine to one of skill in the art to screen whether an expression vector or peptide has the desired characteristics; the prior art cited by the Examiner demonstrates that

gene therapy works and does not support the unpredictability of gene therapy; and one of skill in the art would know what cell surface receptors to phenotypically knock-out in the extensive list of diseases claimed, in order to provide treatment.

These arguments are not persuasive, individually or in total, for the following reasons. First, it is noted that the enablement rejection set forth in the previous action and maintained herein did not rely solely on the lack of a working example, but relied properly on the analysis of all the Wands factors and is based on the evidence as a whole. Second, while it is true that there is no requirement for a working example for a specification to be enabled, in an unpredictable field such as the chemical arts and more specifically, gene therapy, lack of a working example *is* a factor to be considered. MPEP §2164.01(c). Applicant states there is extensive reduction to practice and points to 1) an example showing targeting cytokines to specific intracellular locations; 1) phenotypic knock out of CCR5 and CXC4 receptors and subsequent inhibition of HIV-1 infection; and 2) preventing infection by providing human peripheral blood lymphocytes (PBLs) transfected to express intrakines and demonstrating these transformed PBLs are resistant to M-tropic and T-tropic HIV-1 infection. All of these examples are done in vitro (i.e. cell culture). None of these in vitro assays can be extrapolated predictably to an in vivo therapeutic application for preventing HIV infection or for delaying disease progression in an HIV patient. The in vitro assays are essentially a closed system; they lack the subtle yet complex interactions present in vivo. Thus one cannot predict what will happen in vivo based on the closed system in vitro assays. With regard to the third example pointed out by Applicant, it is important to clarify that Applicant has *not* shown

that one can prevent infection using the transformed cells in a patient or that disease progression can be delayed using such cells transformed into an HIV patient; this statement is merely an assertion of what the Applicant hopes will occur. Moreover, the extensive disclosure of techniques and assays in the specification does not address the expert-acknowledged major obstacles of gene therapy set forth in the previous action: gene delivery and sustained expression of the gene. Likewise, the assertion that it is routine to one of skill in the art to screen whether an expression vector or peptide has the desired characteristics is not directly relevant as these are not the major obstacles of gene therapy. The scope of Applicant's claims encompasses in vivo transformation which raises the problems of efficient and specific gene delivery. Sustained expression of the gene, the receptor binding polypeptide fusion protein, is a problem in all of the claimed embodiments.

Applicant does not understand the Examiner's assertion that the claims are broad as there is no prohibition against broad claims. While it is true that there is no prohibition against broad claims, enablement must be commensurate with the full scope of the claims. Thus, broad claims necessitate a more substantial disclosure for enablement, particularly in unpredictable arts such as the chemical arts.

Applicant's assertion that Verma et al demonstrates that gene therapy works is not persuasive as it is not entirely accurate. Applicant states that Verma et al demonstrated continues expression of an exogenous nucleic acid encoding Factor IX at high levels for more than two years in mice and that alternatives to overcome the problems of express were known. Applicant has overlooked the context of Verma's

statement. Verma et al follow this statement with "But the search for such [appropriate enhancer-promoter combinations] is a case of trial and error for an given cell type" (p. 240, bridge of second and third columns). In other words, specific alternatives were not in fact known to overcome the sustained expression problems but in fact would be the subject of trial and error experimentation to ascertain. Such trial and error experimentation, in view of the enormous number of cells types encompassed by Applicant's claims, would be undue experimentation for one of skill in the art to undertake in order to use the claimed invention.

Applicant states that the Fox reference does not support the lack of enablement rejection or the unpredictability of the art of gene therapy. Applicant concludes that gene therapy techniques have been used extensively with only rare critical setbacks. While various gene therapy techniques have been used in clinical trials extensively, there have been a positive therapeutic result has been very, very rare. Thus, the prediction of the prior art with regard to gene therapy is that is will not work.

Applicant asserts that the Examiner is issuing a 35 USC §101 lack of utility rejection under the guise of an enablement rejection. Applicant is mistaken. The rejection set forth in the previous action is quite clearly and properly a rejection under 35 §112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or ***use*** the invention. Applicant has not enabled the in vivo gene therapy-based therapeutic methods, the sole disclosed use for

the vectors and methods in the instant claims. Therefore, the use is not enabled and the appropriate rejection was rendered.

Applicant asserts that one of skill in the art would know what cell surface receptors to phenotypically knock-out in the extensive list of diseases claimed to provide treatment. This assertion is apparently the opinion of Applicant's representative. There are no references provided to support the assertion. Neither the specification nor the prior art disclose the cell surface receptors and the associated ligands for any disease other than HIV.

Applicant argues that it is not undue experimentation where one of skill in the art routinely assays compounds for the asserted utility, citing *In re Wands*, *In re Angstadt* and *In re Bundy*. Routine assays are not undue experimentation, however, Applicant asserts that routine screening that identifies expression vectors encoding chemokines can intracellular bind chemokine receptors and inhibit chemokine receptor transport to the cell surface, leads to enabled gene therapy applications for these vectors. This the unproven and unpredictable leap from in vitro evidence that expression vectors encoding chemokines can intracellular bind chemokine receptors and inhibit chemokine receptor transport to the cell surface, that such expression vectors could be used without further experimentation to treat or inhibit HIV infection or any of the other claimed diseases. As discussed above, all the examples are done in vitro and the in vitro data does not correlate with in vivo data as it fails to replicate the complexity of in vivo systems. As set forth in the previous office action, there is extensive experimentation necessary to enable the claimed subject matter. One of skill in the art

would have to determine which specific cell surface receptor mediates which of the plethora of claimed diseases, what ligands binds specifically and solely to each so-identified cell surface receptor, what effect exogenous transgene expression encoding a cell surface receptor binding polypeptide would have in any cell type, whether the effect could be exploited for treatment or prevention of a disease, how to deliver the nucleic acid to the appropriate target cells with specificity and efficiency and how to get sufficient, sustained expression to induce at least some therapeutic effect. With regard t treatment of an HIV infection, one of skill in the art would have to determine what effect exogenous transgene expression would have in T4 cells and macrophages, whether the effect could be exploited for treatment of HIV, how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. Answering all of these questions requires a large quantity of trial and error experimentation by the skill artisan which raises the level of experimentation far beyond the "routine level" asserted by Applicant.

The rejection is therefore maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 19 is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is based on the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. §112, first paragraph "Written Description" Requirement published in the Federal Register (Volume 66, Number 4, Pages 1099-1111). Claim 19 is drawn to a method of inhibiting phenotypic expression of a chemokine receptor by expressing one or more receptor binding polypeptides including a chemokine analog. This is a genus claim in terms of chemokine analog. The specification mentions ΔRANTES, which has a deletion in its N-terminus of amino acids 2-8 a chemokine analog, as well as a reference (Arenzana-Seisdedos et al; note that this author's name is misspelled in both the specification, now corrected by informal Examiner's amendment, and in Applicant's amendment filed 31 January 2002) which deletes the first amino acids of RANTES. This disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envision all analogs based on the teachings in the specification. The specification appears to define a chemokine analog as maintaining receptor binding but lacking biological activity. Only one specific species, ΔRANTES, is disclosed. However, the specification does not teach a structure-function relationship for chemokines. There is no disclosure of what sequences are necessary for formation of the hydrophobic core of the protein and thus

structural integrity, what sequences are necessary for receptor binding and what sequences are necessary for biological activity other than receptor binding. It is also unclear that N-terminal deletions of up to 8 amino acids in any chemokine will yield a "chemokine analog". Therefore, the specification does not describe the claimed chemokine analogs in such full, clear, concise and exact terms so as to indicate that Applicant has possession of these chemokine analogs at the time of filing the present application. Thus, the written description requirement has not been satisfied.

8. Claims 1-16, 18-22, 29, and 33-39 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to an expression vector comprising a chemokine encoding gene. Claim 18 is drawn to a method of inhibiting phenotypic expression of a chemokine receptor comprising a vector comprising a chemokine receptor binding polypeptide gene. Claim 29 is drawn to a method of inhibiting HIV infection of a cell wherein the cell is transduced with a chemokine gene fusion. Claim 35 is drawn to an expression vector comprising a chemokine encoding gene. "Gene" refers to an entire genomic structure encompassing all the regulatory regions (5" untranslated and 3' untranslated regions) as well as exons and introns. A representative number of eukaryotic genes for receptor binding polypeptides or chemokines is not known. Thus,

the written description requirement has not been satisfied with respect to the word "gene".

This rejection would be overcome by amending the claims to recite "coding region".

9. The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-16 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 1 recites the limitation "the expression region" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

Claims 1-24, 29 and 33-39 are rejected. Claims 1-24, 29 and 33-39 are free of prior art.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from

10:00 AM to 6:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Tracey Johnson, Patent Analyst whose telephone number is (703) 305-2982.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

April 22, 2002

REMY YUCEL, PH.D
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